2,6 Diethyl Aniline and Ortho ethyl aniline: Ring-substituted Monocyclic Aromatic Amines Category Justification and Testing Rationale

CAS 57466-8 and 578-54-l
(Plus SIDS/ICCA Chemicals 62-53-3 and 2454906-2 for reference)

I. INTRODUCTION

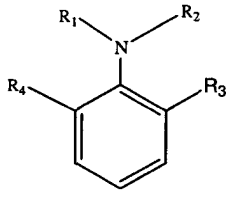
Albemarle Corporation (Albemarle) would like to submit a test plan for 2,6 diethyl aniline (2,6 DEA) in the Environmental Protection Agency's High Production Volume (HPV) Challenge Program and for ortho ethyl aniline, listed as an Extended High Production Volume chemical.

Albemarle is committed to making existing test data publicly available for these chemicals and to develop any additional screening level data needed on health and environmental effects, fate, and physiochemical properties. In order to minimize the use of animals in the testing of chemicals, Albemarle has conducted a thorough literature search for all available data, published and unpublished for 2,6 DEA and related alkyl substituted aromatic amines. It also has performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information as appropriate. No testing of whole animals is proposed. This document describes the alkyl substituted aniline 2,6 DEA, included in the HPV program, ortho ethyl aniline (OEA), included as an "Extended HPV" chemical and notes the related chemicals that are being sponsored through the OECD SIDS program (aniline, 2,6 MEA). This is similar to the approach used by the Monocyclic Aromatic Amines and Nitroaromatics (MAANA) Panel and its member companies for monocyclic aromatic amines with nitrogen substituents previously. Data on all these chemicals are included to provide justification for the proposed category. Robust summary documents have been prepared and are included for each of these chemicals (aniline document from the MAANA panel, 2,6 methyl ethyl aniline IUCLID from the European Chemical Bureau files). Finally, the rationale for proposed testing is described.

II. DEVELOPMENT OF THE Ring-substituted Anilines CATEGORY

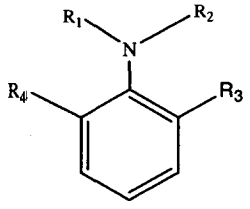
All chemicals included in this plan are monocyclic aromatic amine compounds, with aniline as the parent chemical. These substituted anilines all have a single amino group and also have one or more methyl or ethyl substituents on the aromatic ring. Figure 1 gives the names, CAS numbers, and structures of the compounds in the HPV program. Other chemicals in this category are scheduled for review under the ICCA program and are undergoing or have undergone review in the OECD SIDS program. The data from these chemicals provides a more complete understanding of this category, and they are listed in Figure 2.

Figure 1. Ring-substituted Anilines Included in the HPV Program



Chemical Name	CAS Number	R1	R2	R3	R4	Program
2,6 Diethyl Aniline	579-66-8	H	H	C_2H_5	C_2H_5	HPV
Ortho Ethvl Aniline	578-54-I	H	H	C_2H_5	H	Extended HPV

Figure 2. Related Anilines



Chemical Name	CAS Number	R1	R2	R3	R4	Program
2,6 Methyl Ethyl Aniline	24549-06-2	H	H	CH_3	C_2H_5	OECD SIDS
Aniline	62-53-3	H	H	H	H	OECD SIDS

Manufacturing, Use and Exposure Information on Ring-substituted Anilines

2,6-DEA is a representative ring substituted aniline prepared by ot-thoalkylation chemistry. This process involves the reaction of aniline with ethylene catalyzed by aluminum anilide catalyst. The catalyst is prepared by the reaction of aniline with triethylaluminum.

The largest category of use for these chemicals is as chemical intermediates in the synthesis of a variety of organic chemicals. Because the majority of the production volume is converted to other chemicals (i.e., is used as a chemical intermediate), human and environmental exposure to the original chemical is limited. 2,6 Diethyl aniline has been reported to be an intermediate for the manufacture of agriculture products, dyestuffs, antioxidants, pharmaceuticals, synthetic resins, fragrances and other products (Kuney, JH ed, 1992). 2,6 DEA is used in the production of triazine herbicide. (Kirk-Othmer, 1991). OEA has been reported to be used as an intermediate for pharmaceuticals, dyestuffs, pesticides and other products (Lewis, RJ, ed, 1997)

Because of their use as chemical intermediates, the potential for exposure exists primarily in the workplaces of the manufacturers and their customers. The manufacturers use and recommend both personal protective equipment and engineering controls. Splash-proof chemical safety goggles, full-faceshields, or full-face respirators are recommended to protect against eye contact. Local exhaust ventilation is recommended to minimize inhalation exposure. Organic vapor cartridge respirators are recommended for use if there is a potential for exposure to vapors or mists. In case of a spill or leak, appropriate protection, which may include a respirator with supplied air, is required. Appropriate gloves, aprons, and chemical resistant clothing are used to prevent dermal contact.

Test Plan Rationale

There is a large amount of test data available for the sponsored HPV substituted anilines and the other related anilines. These data allow the use of categories and estimation to predict effects where data are missing. The summary documents enclosed for each chemical summarize the available studies. The critical studies to fulfill required HPV Challenge endpoints were chosen according to several factors, including documentation and detail, when the study was conducted, and access to a detailed publication or report. Overall, existing data has been identified for all of the HPV Challenge endpoints.

Physical and Chemical Properties

The physical and chemical properties of all the chemicals in the category are summarized in Table 1 below. All the compounds are liquids at room temperature, with relative densities ranging from 0.967 to 1.02. The boiling points all range from 184°C (aniline) to 241 °C (2,6 DEA). The vapor pressures at 25 °C range from is from 0.0038 mm Hg for 2,6 DEA to an estimated value of 0.49 mm Hg for aniline. The water solubility estimates range from less than 1 g/L for the substituted anilines to 36 g/l for aniline. The range of the log of the octanol-water partition coefficients is from 0.91 (aniline) to the estimate of 3.15 for DEA. These data are sufficient to describe the properties of this category, and no further testing is proposed.

Table 1: Data Values: Physical and Chemical Properties

	Aniline 62-53-3	2,6 Diethyl aniline 579-66-8	2,6 methyl ethyl aniline 24549-06-2	Ortho ethyl aniline 578-54-1
Molecular Weight	93.13	149.24	135.21	121.18
Melting Point (°C)	-6.2	3.5	-33 40.13 (est)	-46.5 22.88 (est)
Boiling Point (°C)	184.0	231 241 (est)	231 at 1013 hPa	209.65 223.43 (est)
Density g/cc at 20°C	1.0213	0.959	0.97	0.98
Vapor Pressure	0.49 mm Hg at 25°C	0.00383 mm Hg at 25°C	0.063to 0.8 hPa at 20°C 0.0742 mmHg (est)	0.17 mmHg at 25°C 0.22 (est)
Log P	0.9 1.08 (est)	0.95 3.15 (est)	2.66 (est)	1.74 2.11 (est)
Water Solubility	36 g/l at 20°C	670 mg/l (est)	2.66 g/l at 22°C 467.3 to 704.86 mg/L at 25°C (est)	416 to 3245 mg/l (est)

(est) – EPIWIN Model Estimate

Metabolism

Metabolism of arylamines generally proceeds through N-oxidation, hydroxylation of aromatic ring carbons, and formation of conjugates such as glucuronides, sulfates, and acetates to expedite elimination (Kharchevnikova and Zholdakova, 1997; Cheever et al, 1980; Son et al, 1980). Ring alkyl substituents may also be oxidized to alcohols and further metabolized to acids (Son et al, 1980). N-Oxidation is an important step that can lead to the formation of metabolites that will react with cellular macromolecules (Kiese, 1963; Burstyn et al, 1991; Garner et al, 1984). The N-phenylhydroxylamines and nitrosobenzenes produced by N-oxidation are capable of binding to the heme ion in hemoglobin and causing oxidation. This reaction can produce the methemoglobinemia that is the most typical toxicity associated with aromatic amines. Aniline itself is oxidized primarily to o- and p-aminophenol. These metabolites are subsequently conjugated with glutathione to form o- and p-aminophenylmercapturic acids for urinary excretion (Radomski, 1979; Baranowska-Dutkiewicz, B, 1982; Irons et al, 1980; Williams, 1959; Parke, 1960).

The most common metabolic reaction for the toluidines is ring hydroxylation. o-Toluidine undergoes hydroxylation in the para position, as well as a lesser amount of N-acetylation, and conjugation with sulfates and glucuronides (Cheever et al, 1980; Son et al, 1980). Ortho ethyl aniline should undergo similar hydroxylation.

Metabolic studies of 2-ethyl 6-methyl aniline in rats, using oral, dermal and inhalation routes showed rapid excretion, primarily by the kidney. The major metabolite in the urine was the sulfate ester conjugate of 2-ethyl-4 hydroxy-6-methyl aniline. It represented 65% (oral, low dose), 77% (oral, high dose), 60% (dermal) and 51% (inhalation) of the dose given. (Hambock, H, 1982 – see 2,6 MEA IUCLID)

Metabolic studies are available for 2,6 DEA. Oral or dietary doses in rats showed that for 2,6 DEA, the urine was also the major metabolic route of elimination. Male rats eliminated 54.6 to 73.6% (Long Evans versus Sprague Dawley rats) in the urine from dietary exposure, and 49-9 to 66.6% after gavage dosing. Female rats after gavage dosing eliminated 70.4% via the urine.

Incubation of 2,6 diethylaniline with NADPH microsomes produced 4-amino-3,5-diethylphenol as the major incubation product. The phenol undergoes further oxidation to 3,5 diethyl-benzoquinone-4-imine, which is isolated as a minor metabolite during 2,6-diethylaniline metabolism (Snyder, R., ed., 1990)

Fate

The data values for environmental aspects are summarized in Table 2 below.

In general, anilines absorb light in the environmental UV spectrum (> 290 nm). Thus, 2,6 DEA is expected to absorb light and may potentially undergo direct photolysis. However, 2,6 DEA is not predicted to partition to the air in significant amounts. Due to the low vapor pressure, the 2,6 DEA that does occur in the ambient atmosphere will be in the vapor phase. Vapor phase 2,6 DEA is predicted to degrade in the atmosphere by reaction with photochemically-produced hydroxyl radicals. The half-life for this reaction in air is estimated to be 0.792 hours, calculated from it's rate constant of 1.6 x 1 O-l 0 cu cm/molecule-set at 25°C. OEA, has an estimated half-'life for the same reaction of 0.971 hours.

If released into water, biodegradation is a major removal process for aniline. A short acclimation period generally enhances biodegradation of aniline. Biodegradation has been studied extensively for aniline – it is even used as a reference chemical in ready biodegradation testing to validate the testing system.

However, the substituted anilines can be predicted to not readily biodegrade, using environmental modeling tools. This is demonstrated by biodegradation testing of 2, 6 methyl ethyl aniline, where values of 0 to less than 10% biodegradation has been seen in ready biodegradation tests (OECD 301 D and E).

Based on estimated log Koc values, the substituted anilines would be expected to have slow to moderate migration through soils and low to moderate sorption to soils. However, aromatic amines (including aniline) bind to humic material in two phases (a rapid, equilibrium phase, and a slower, less reversible phase) which could decrease movement in soil. (Parris, GE, 1980).

Adsorption to sediments is predicted to be low for all these aromatic amines, but the protonated forms of these chemicals will bind more strongly. Aniline with a pKa of 4.6 will exist partially in the protonated form in aqueous environment, and the protonated form of aniline is not expected to volatilize from water. In moist soils, the protonated form will bind strongly to soil surfaces. Ortho ethyl aniline has a pKa of 4.3 also will partially exist as the protonated form, which will bind to soil surfaces and not volatilize. 2,6 DEA would react similarly.

None of the ring substituted anilines is likely to bioaccumulate in aquatic organisms, based on the estimated octanol-water partition coefficients. Measured BCF values of less than 10 in fish suggests that bioconcentration of aniline in aquatic organisms is low. Estimated BCF values for the substituted anilines are from 4.4 (OEA) to 53 (DEA). Lack of bioaccumulation has been demonstrated for 2,6 DEA in fish, where the bioconcentration factor was found to be 120.

If released into soil, leaching and reaction with organic constituents are expected to be major removal processes. Binding to soil is predicted to be low to moderate, and as for sediments, binding will vary with pH and humic material. Evaporation from dry soil is expected to be low, because of low estimated vapor pressures.

Degradation in soil systems is also likely. 2,6 DEA is degraded by soil microorganisms such as Chaetomium globosum (Snyder, 1990), and in nonsterile soils, 40-75% of applied DEA can disappear in 20 hours. These transformation rates are affected by pH – increasing transformation with acidity (Bollag, JM, 1987). When tested in an enclosed aquatic system containing planktons, insects and snails, 2,6 DEA was considered readily biodegradable based on the organisms abilities to quickly eliminate it (Lu, PY, 1974).

There are sufficient data for these substituted anilines to characterize the fate of these chemicals. None of the substituted anilines meet the criteria for Persistent, Bioaccumulative and Toxic (PBT) chemicals, and no further testing is proposed.

Aquatic Toxicity

In most acute toxicity tests, the 2,6 DEA and the related compounds were harmful to fish (96-hr LC50 values >10 mg/L <100 mg/L. Experimental data was available for several fish species for 2,6 DEA (24-30 mg/l 96 hour LC50 values), and estimated for OEA (30.2 mg/L).

Ring substituted anilines in the category were harmful to algae (similar to aniline), or not tested. 2,6 DEA has not been tested, but is predicted to be similar to MEA (58 mg/L over 5 days) and OEA (38 mg/L).

Invertebrate toxicity values range from 0.25-3 mg/l LC50 at 48 hours for aniline to 21 mg/l (DEA). MEA and OEA have also been tested in Daphnia, with LC50 values of 12.8 to 13.5 for MEA and 8.05 for OEA.

There is a large amount of aquatic toxicity data available on chemicals in this category, and no further testing is proposed.

Table 2: Data Values: Environmental Aspects

	Aniline 62-53-3	2,6 Diethyl aniline 579-66-8	2,6 methyl ethyl aniline 24549-06-2	Ortho ethyl aniline 578-54-1
Environmental Fate				
Photodegradation	Air partitioning likely low	Air partitioning likely low	Air partitioning likely low	Air partitioning likely low
Indirect photolysis, rate constant cm^3/ (molecule * sec)	1.1 - 1.18 x 10^{-10} (measured)	1.62 x 10^{-10} (estimated)	1.62 x 10^{-10} (estimated)	1.32 x 10^{-10} (estimated)
Hydrolysis	11.3% (pH 6, 30'C) after 48 hours	Lacks functional groups likely to hydrolyze	Lacks functional groups likely to hydrolyze	Lacks functional groups likely to hydrolyze
Distribution (PBT profiler)	Air: 0% Water: 45% Soil: 54% Sediment: 0%	Air: 0% Water: 19% Soil: 80% Sediment: 1 %	Air: 0% Water: 22% Soil: 78% Sediment: 0%	Air: 0% Water: 37% Soil: 63% Sediment: 0%
Biodegradation % biodegradation/days	92-97%/ 6 days	Not expected to readily degrade	0-10%/ 28 days	Not expected to readily degrade
Log Koc	1.65 (est)	2.659 (est)	2.374 (est)	2.155 (est)
Ecotoxicity				
Acute fish LC50, 96 hours	ca 10 ppm	30.2 (est)	13.2 (est)	30.2 (est)
Winter flounder	--	29 mg/l	35 mg/l	--
Trout	8.2 mg/l a	24 mg/l	43-1-44 mg/l	--
Bluegill	--	30 mg/l	--	--
Acute invertebrate LC50, 48 hours	0.25-0.3 mg/l	21 mg/l	12.8-13.5 mg/l	8.05 mg/l
Acute algal, EC50	19 mg/l 96 hr 94-175 mg/l 72 hr	--	58 mg/l (5 days)	38 mg/l
Bioaccumulation: BCF Estimated or experimental	2.6 (exp)	53 (est) 120 (exp)	22 (est)	4.4 (est)

a Abram, et al, 1982.

Mammalian Acute Toxicity

The data values for toxicity are summarized in Table 3 below. The ring substituted anilines have been tested for acute toxicity. All can be considered harmful by single oral doses, as the rat oral LD50's are generally >500 to > 2000 mg/kg. There is a single oral LD50 value for 2, 6 DEA of 2690 mg/kg. increasing alkyl substitution on aniline appears to lessen the acute oral toxicity.

In a study of the effect of substituents on acute rat toxicity in mono- and di-alkyl ring substituted derivatives of aniline, Jacobson (1972) found that the alkyl substituted anilines were less acutely toxic than aniline, and that length of chain (Cl to C3) on a single e-substituted aniline does not change toxicity, but that toxicity decreases with increasing chain length on the 2,6 disubstituted anilines.

Comparison of LD50 and Substituent Group of Aniline Derivatives

	LD50 (g/kg)	
Alkyl group	2-alkyl	2,6 dialkyl
Methyl	0.90	0.84
Ethyl	1.26	2.69
Isopropyl	1.18	4.27

The rabbit dermal LD50's for the disubstituted compounds are > 1000 mg/kg by single dermal applications. Ortho ethyl aniline had a dermal LD50 value of 840 mg/kg, more like aniline (820 mg/kg and lower values reported) Where systemic toxicity was found, all these compounds caused cyanosis and increased respiratory rate from methemoglobinemia. These material are irritant to they eyes, and can cause irritation of the skin. No further testing is proposed for the ring substituted anilines for acute toxicity.

Mammalian Repeated Dose Toxicity

Oral or inhalation repeated exposure studies have been completed on 2,6 DEA, aniline, and 2,6 MEA. In a direct comparison, aniline, o-toluidine, 2,6 DEA, and 2,6 MEA and other anilines were given orally to rats for 5, 10, or 20 days at one-fourth of the LD50. Histopathology examinations found splenic congestion, increased hematopoiesis, hemosiderosis, and periacinar vaculolar changes in all. (Short et al, 1983).

2,6 DEA has been tested by repeated dose exposure by oral, dermal, inhalation and dietary routes, and has included rat, dog, and rabbit species. Studies have ranged in length from 28 day, to 90 day to lifetime chronic toxicity studies.

Based on the length of studies, the multiple routes and species, as well as consistent acute results for all the compounds, no further repeated exposure testing is proposed.

Genetic Toxicity

Standard bacterial mutagenicity assays with and without metabolic activation have been conducted for aniline and the ring substituted anilines considered. Aniline has shown positive results in some Ames tests. 2,6 DEA, 2,6 MEA and OEA, for the most part, have negative Ames test results. 2,6 DEA and 2,6 MEA showed weak positive reactions in tester strains T98 and T1 00 with activation. In these cases, increase in revertants in those strains were no more than twice that of negative controls.

In Vivo, 2,6 DEA and 2,6 MEA did not induce micronuclei in the mouse micronucleus assay. Aniline was negative in a dominant lethal assay.

No further testing is proposed for genetic toxicity for this group.

Table 3: Data Values: Toxicity

Mammalian Toxicity				
Acute toxicity: Oral, rat, LD50	440-750 mg/kg	2690 mg/kg 1800 mg/kg	885, 1180, 1150, 1200 mg/kg	1260 mg/kg
Dermal, rabbit, LD50	820-1540 mg/kg	1100 mg/kg	1290 mg/kg	840 mg/kg
Inhalation, rat, LC50 4 hours	550 ppm	> 33 ppm	> 260 ppm	> 65 ppm (1-4 hours)
Skin irritation	Mild	Moderate	Not irritating	Not irritating
Eye Irritation	Irritant	Irritant	Irritant	Irritant
Repeated dose toxicity Oral route, length	20 day	20 day	20 day	C
Dietary route, length	24 months	28 and 90 day		
Dermal route, length		28 day		
Inhalation route, length	14 days	30and 90day		
Genetic toxicity				
in vitro: gene mutation Bacteria: Ames test	Positive	Negative most T weak +T98T100	Negative (two) weak +T98,T100 in one test	Negative
in vitro: chromosome aberrations Cytogenetics, CHO or CHL	Weak + with activation			Negative
in vitro: cell transformation				C
SHE cells	Negative			
BALB3/C3 cells	Positive	Negative	Negative	
in vivo:				C
Micronucleus	Most Positive	Negative	Negative (two)	
Cytogenetics, rodent	Negative	Negative		
Dominant Lethal, rat				
Carcinogenicity				
Rat	+ Spleen	Negative	C	C
Mouse	Negative			
Reproductive toxicity	P	P	C	C
Developmental toxicity	Negative, rat	Negative, rat	C	C

C = Use of Category Approach
P = >90 Day study found no pathology of reproductive organs

Developmental and Reproductive Toxicity

A full developmental toxicity study in rats for 2,6 DEA found fetotoxicity at maternally toxic doses, but no evidence of teratogenicity or embryotoxicity. Other compounds in the category have also been tested for developmental toxicity. A full developmental toxicity study of aniline failed to find evidence of a teratogenic effect.

Consideration is given to effects on reproductive organs in repeated exposure studies to determine whether further reproductive toxicity studies are needed. 2,6 DEA was tested in repeated dose studies ranging from 28 days (dietary and dermal routes), 90 days (dietary and inhalation), and 24 months (dietary) in length. Subchronic and chronic studies of aniline in rats and mice found no evidence that reproductive organs would be affected.

A dominant lethal study of aniline in rats was also completed to address the possibility of heritable effects being transmitted to the offspring from parental males. No dominant lethal effect was found in the rat. In keeping with the lack of heritable genetic damage from aniline exposure.

As the substituted anilines are covered by the subchronic, chronic, and developmental data discussed above for these and related aromatic amines, no further testing for reproductive toxicity is proposed.

The existing data summary and proposed test plan are summarized in Table 4 below.

Table 4. Summary of Data Gaps and Method of Completion

	Aniline 62-53-3	2,6 Diethyl aniline 579-66-8	2,6 methyl ethyl aniline 24549-06-2	Ortho ethyl aniline 578-54-1
Environmental Fate				
Photodegradation	A	S	S	S
Hydrolysis	A	C	C	C
Fugacity	S	S	S	S
Biodegradation	A	S	A	S
Ecotoxicity				
Acute fish	A	A	A	S
Acute invertebrate	A	A	A	A
Acute algal	A	C, S	A	A
Mammalian Toxicity				
Acute toxicity	A	A	A	A
Repeated dose toxicity	A	A	A	C
Genetic toxicity				
in vitro: gene mutation	A	A	A	A
in vitro: chromosome aberrations	A	A	A	C
in vitro: cell transformation	A	A	A	C
in vivo: chromosome aberrations	A	A	A	C
Reproductive toxicity	P	P	C	C
Developmental toxicity	A	A	C	C

= ICCA and OECD SIDS chemicals (testing will be addressed under ICCA HPV Program)

A = Adequate data available
T = Testing to be done
NG=Non-guideline data available
S = Structure-activity relationship (modeling program used)
C = Use of Category Approach
P = >90 Day study found no pathology of reproductive organs

Aniline Category References:

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